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Glycopeptide Antibiotics in the Era of Resistance: An Updated Overview

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Abstract: Glycopeptide antibiotics are a family of antimicrobials that function primarily by sharing a similar macromolecular structure. The second commercially available glycopeptide antibiotic is tecoplanin, a ristocetin-type lipoglycopeptide molecule originally discovered in 1978 from the Actinoplanes teichomyceticus. Outside the cell membrane, peptidoglycan, or murein, provides structural support for the bacterial cell wall. Polypeptide and disaccharide units are connected on a sugar backbone by glycosidic bonds in peptidoglycan monomers, which allow for the formation of long chains by transglycosylation. Three novel lipoglycopeptides are now undergoing clinical trials: oritavancin, dalbavancin, and telavancin. Vancomycin is effective against a wide variety of streptococci, including those with viridian, anaerobic, or microaerophilic characteristics, and against penicillin-sensitive or -resistant pneumococci.

Keywords: *Glycopeptide Antibiotic, Teicoplanin, Vancomycin, Methicillin-Resistant Staphylococcus Aureus, Teicoplanin.*

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I. INTRODUCTION

Glycopeptide antibiotics are a family of antimicrobials that function primarily by sharing a similar macromolecular structure. Tolerance, efficacy, and pharmacokinetic improvements have allowed most lipoglycopeptides to evolve from vancomycin. These drugs are comparable to vancomycin in their antibacterial capabilities. They are effective against several different types of bacteria, including methicillin-resistant Staphylococcus aureus, Enterococcus, and Streptococcus. During development, these macromolecular glycopeptides bind to peptidoglycans in the bacterial cell wall, preventing the cell wall from forming.[1] The lipoglycopeptides have a long half-life when administered intravenously and are not absorbed when taken orally; thus, they can be given once a day or even once a week. Compared to its more modern lipoglycopeptide counterparts, vancomycin boasts a longer license history, a broader variety of uses, and a superior safety record, all while being a glycopeptide. Glycopeptide antibiotics, which are large semisynthetic compounds chemically linked to vancomycin, have the potential to kill gram-positive bacteria, including Methicillin-resistant Staphylococcus aureus (MRSA). The United States has licensed the use of three lipoglycopeptide antibiotics: telavancin, oritavancin, and dalbavancin. Treatment with any of these three drugs has been associated with transient increases in blood enzyme levels; however, no evidence has connected any of these drugs to acute liver damage.[2]

II. HISTORY OF GLYCOPEPTIDE ANTIBIOTICS

The first two glycopeptide antibiotics, ristocetin and vancomycin, were found in the middle of the 1950s by Abbott Laboratories and Eli Lilly. They were derived from actinobacteria, namely Amycolatopsis orientalis. While both were used to treat Gram-positive infections in the clinic, ristocetin was discontinued due to the risk of thrombocytopenia in select susceptible individuals. The structure of vancomycin was finally determined in 1982, a full 27 years after the drug's first human administration in 1955, even though it had been authorised for clinical use in 1958.[3] The usage of vancomycin began to decrease in the 1980s, when the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in hospitals began to rise. This occurred because a newer generation of antibiotics was introduced. Clinicians relied on vancomycin as their go-to medication until reports of widespread resistance surfaced. Notable because its limited use has prevented widespread glycopeptide resistance, this is an important development. The second commercially available glycopeptide antibiotic is tecoplanin, a ristocetin-type lipoglycopeptide molecule originally discovered in 1978 from the Actinoplanes teichomyceticus. Several nations have used tecoplanin since

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it was authorised in 1998 by the European Union. However, the US government has never authorised its usage. The long period that passed between the discovery of vancomycin and the development of resistance, its remarkable therapeutic efficacy, and its inability to produce resistance in other classes of antibacterial drugs all contributed to a surge in interest in discovering new GPAs derived from natural compounds.[4] The development of current glycopeptide medicines was helped forward by a surge in the discovery of novel glycopeptides from 1982 to 1996. This growth was facilitated, in part, by advancements in spectroscopy, which allowed for the rapid identification of structural components. Consequently, there was a surge of interest in the subject. However, there has been a slowdown in the rate of novel glycopeptide discoveries since the mid-1990s; therefore, innovative methods to isolate and purify the actinomycete strains responsible for these compounds have been required. Rather than a substantial rise in naturally occurring glycopeptides, semi-synthetic or genetically designed alternatives have been developed as a result of these breakthroughs. Pekiskomycin was discovered in 2013 by Wright and colleagues using a novel resistance screening and genomics approach. This is an exception worth mentioning. We developed and validated a novel approach that integrated a glycopeptide resistance prefilter with a technique for screening for novel biosynthetic gene clusters; this helped with the first selection of isolates.[5]

- *Chemical Structure and Structure-Activity Relationships*

The initial natural products were glycopeptides, but in the last 20 years, researchers have learnt to grasp the relationships between structure and activity, which has allowed them to create semi-synthetic derivatives with improved pharmacokinetic characteristics and activity. A "glycopeptide" is a cyclic peptide, which is a protein with two carbohydrates and seven amino acids. In order to bind to its target, the D-Ala-D-Ala termini of peptidoglycan precursors, the antibiotic creates five hydrogen bonds with the drug's peptidic backbone. The creation of homodimers is facilitated by itavancin and other drugs that include additional chlorine and/or sugar. As a result, goal-specific coordination binding is achieved. To enhance their antibacterial effect and lengthen their half-life, teicoplanin and all of its semi-synthetic derivatives possess a lipophilic side chain.[6]

III. THE MECHANISM OF ACTION

Outside the cell membrane, peptidoglycan, or murein, provides structural support for the bacterial cell wall. Polypeptide and disaccharide units are connected on a sugar backbone by glycosidic bonds in peptidoglycan monomers, which allow for the formation of long chains by transglycosylation. Antibiotics derived from glycopeptides can penetrate cell membranes and make noncovalent interactions with the terminal carbohydrates at the polymerisation site. The transpeptidase is then prevented from cross-linking by this. Cytolysis and cell death occur as a result of the compromised cell wall's inability to withstand the internal positive osmotic pressure. Gram-positive bacteria are unable to produce cell walls when exposed to vancomycin. Vancomycin does not work against gram-negative bacteria (except a few nongonococcal Neisseria species) because these bacteria have a wide variety of cell wall production mechanisms and a wide variety of factors that influence how well their outer membranes penetrate.[7] According to theoretical and experimental evidence, vancomycin forms five hydrogen bonds between the glycopeptide backbone and the D-Ala-D-Ala residues at the D-Ala-D-Ala terminal of pentapeptidic precursors, its primary binding site. This drug employs steric hindrance to halt transpeptidation reactions. The importance of vancomycin's protonated state and the synthesis of glycopeptide antibiotic dimers during this interaction has been brought to light by recent investigations. Microbes that are vulnerable to teicoplanin are unable to develop cell walls. It is difficult for bacteria to produce peptidoglycans in their cell walls due to nonspecific binding and saturation of their exterior peptidoglycan layers. Teicoplanin binds to precursors through a cleft that accommodates its D-Ala-D-Ala terminus. The antibiotic teicoplanin is effective against a variety of aerobic and anaerobic gram-positive bacteria, much like vancomycin. Tecoplanin sometimes outperforms vancomycin when it comes to treating gram-positive bacteria, such as streptococci. The bactericidal effects of the two medications are comparable, albeit when measured in terms of S. aureus, including methicillin-resistant Staphylococcus aureus; nevertheless, teicoplanin's efficacy against coagulase-negative staphylococci differs. The bactericidal effect of teicoplanin is dose-dependent, and various testing culture media have demonstrated varying degrees of efficacy against various coagulase-negative staphylococci strains. Because it is difficult to develop resistance to both vancomycin and teicoplanin at the same time in the lab, subculturing the bacteria without antibiotics would eradicate any resistance that may develop.[4,7] Oritavancin's enhanced reduction of cell wall peptidoglycan synthesis may be due to its dimerisation capability. It is believed that this occurs as a result of a coordinated binding to the target of the pentapeptide side chain. Peptidoglycan precursors have their steric hindrance intensified by the addition of a large substituent to their disaccharide moiety. Because of this, it is feasible to block the peptidoglycan synthesis-related transglycosylation and transpeptidation reactions. The 4'-chlorobiphenylmethyl group has the potential to dissolve the cell walls of glycopositive bacteria. Staphylococci that are resistant to vancomycin, as well as those that are sensitive to it, exhibit the rapid antibacterial effects of oritavancin. The permeabilization and depolarisation of cell membranes occur simultaneously with these processes, and they are made possible by the attachment of the lipophilic side chain of oritavancin to the cell membrane. Two of telavancin's modes of action include membrane depolarisation and suppression of peptidoglycan production. It impacts the peptidoglycan precursor by binding to the "lipid (undecaprenyl)-linked N-acetylglucosamine-N-muramylpentapeptide" at the D-Ala-D-Ala residues. Inhibited by this interaction are the processes of transglycosylation (peptidoglycan polymerisation) and transpeptidation (crosslinking). While both telavancin and vancomycin are potent inhibitors of peptidoglycan production at the specific transglycosylase, telavancin is ten times more effective in killing entire MRSA cells. The

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bacterial cell membrane interacts with the decyl aminoethyl hydrophobic side chain, which increases the binding affinity of the target area on the surface of the cell for peptidoglycan intermediates.[8] Another property of telavancin is its rapid lowering of the membrane potential, the exact pace of which is concentration-dependent. It appears that the active mechanism is the interaction with peptidoglycan intermediates. The interaction between telavancin and lipid intermediate II molecules may disrupt membrane barrier function and peptidoglycan synthesis, leading to this effect. One possible explanation for telavancin's superior antibacterial efficacy compared to vancomycin is its second mechanism of action, which appears to target bacterial cell membranes rather than mammalian cells. Unlike vancomycin, most of the compounds associated with telavancin are involved in cell membrane maintenance rather than cell wall production. This two-type interaction enhances the carboxylate binding pocket and the terminal D-Ala-D-Ala residues while simultaneously facilitating contact between the decyl aminoethyl side chain and the bacterial cell membrane. Dalbavancin is a lipoglycopeptide that is a member of vancomycin. Dalabavancin, like other glycopeptides, inhibits the synthesis of cell walls, which is how antibiotics like it function. Glycopeptide antibiotics like dalbavancin work by binding to stem pentapeptides in immature peptidoglycans and interfering with cell wall construction processes, including transpeptidation and transglycosylation.[9] This stops gram-positive bacteria in their tracks. The binding of dalbavancin to this substrate inhibits the crosslinking processes that provide the bacterial cell wall with its strength and rigidity. To enhance its stability in the target environment and its affinity for peptidoglycans, dalbavancin dimerises and binds to a lipophilic bacterial membrane. Dallasancin has a prolonged half-life as a consequence of its pharmacologic and pharmacokinetic features, which include increased interaction with the bacterial cell wall.[8,9]

- *Vancomycin*

It was initially discovered that vancomycin was produced by the actinomycete Streptomyces orientalis. The rest of the molecule is composed of a heptapeptide nucleus, aspartic acid, N-methylleucine, three phenylglycine systems, and two chlorinated tyrosines. The molecule becomes cyclic due to two carbon-carbon connections and an ether bond at various points along the heptapeptide backbone. Glucosamine and glucose form a disaccharide, which is absent from the cyclic structure. Vancomycin inhibits cell wall formation by forming a long-lasting, noncovalent complex with the C-terminal D-Ala-D-Ala of murein monomers. Emerging from the bacterial cytoplasm, these monomers are precursor units of peptidoglycans. For these monomers to bind to the expanding peptidoglycan molecule, they typically undergo transglycosylation followed by transpeptidation. To keep the precursor-vancomycin noncovalent complex in situ, the D-Ala-D-Ala residue forms five hydrogen bonds with the amino acids in vancomycin. The complex alters its structure when entering the cell membrane in order to obstruct glycosyltransferase activity. This prevents the precursor molecules from attaching to the peptidoglycan chain that is still in the process of formation. Consequently, transpeptidation is halted, and cell wall production comes to a halt. Bacteria that are dividing are primarily targeted by this inhibitor during the last stages of cell wall production.[10]

- *Teicoplanin*

Fermentation of the actinomycete Actinoplanes teichomyceticus yields teicoplanin, also known as teichomycin A2. This GPA was initially documented in 1978. In terms of structure, chemical composition, and mechanism of action, it is quite similar to vancomycin. A cyclic heptapeptide backbone of aromatic amino acids and two sugar moieties (N-acetyl-beta-D-glucosamine and D-mannose, respectively) make up the complex molecule. One thing that makes it different from vancomycin is the presence of a fatty acid component. This makes the molecule better at penetrating tissues and cells.[11] Three novel lipoglycopeptides are now undergoing clinical trials: oritavancin, dalbavancin, and telavancin. These drugs work primarily by mimicking the action of vancomycin. The molecule can interact with the bacterial cell membrane because of a lipophilic side chain that binds to the lipid bilayer. In this respect, all three lipoglycopeptides are identical. By increasing its affinity for the terminal D-Ala-D-Ala, this enhances the molecule's antibacterial action. In 2005, a hydrophilic (phosphomethyl)aminoethyl group was added to one of the phenylglycine residues, and a lipophilic decylaminoethyl substituent was added to the vancomycin amino group to develop telavancin, a semisynthetic derivative of vancomycin. By enhancing tissue distribution and lowering telavancin elimination, the hydrophilic side chain reduces the risk of nephrotoxicity. Actinomycete species of Nonomura spp. Makes A-40926, an antibiotic that looks like teicoplanin and is a derivative of dallavancin. It was developed in the '90s, but it wasn't until 2014 that it received clinical clearance. A dimethylaminopropanolamine group was added to teicoplanin to become dallavancin by amidating the C-terminal carboxyl group. This modification increases the half-life to almost 300 hours. Oritavancin (LY333328) is the synthetic analogue of the naturally occurring glycopeptide chloroeremomycin, which was also discovered in the 1990s. The vincamine amine is linked to a hydrophobic chlorophenyl-benzyl group, and the phenylephrine hydroxyl group contains an additional aminosugar. Oritavancin is more effective against VRE, especially vanA-generating VRE, due to these structural properties. Because of its hydrophobic side chain and high protein binding, orithanazin has a terminal half-life of over 300 hours.[12]

IV. ANTIMICROBIAL ACTIVITY

Because their size prevents glycopeptides from penetrating Gram-negative bacteria's outer membrane, these molecules are limited to killing Gram-positive and some anaerobic kinds of bacteria.[13]

- *Vancomycin*

The current susceptibility breakpoints in North America are S<2 mg/L, according to the CLSI (www.clsi.org). In Europe, it is S<2 mg/L, and in the West, it is 4-8 mg/L and R>16 mg/L, respectively. It is desired that this value for

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EUCAST will be validated soon, ideally during the proof stage, so that heterogeneously resistant S isolates may be more easily identified. S. S. aureus. Remember that methicillin-resistant Staphylococcus aureus has been on the rise in recent years. It appears that some isolates have managed to keep their MICs below the susceptibility breakpoint while showing an increase of 1-2 mg/L. For further details, read the pharmacodynamics section. This raises doubts about the possibility of therapeutic cures for these strains at normal dosages.[14] Vancomycin is ineffective against mycobacteria, fungi, Bacteroides species, and Gram-negative bacteria except Flavobacterium meningosepticum and a small number of Neisseria species. There is no correlation between S-killing and concentrations of 2-50 mg/L of vancomycin, because the antibiotic kills susceptible bacteria slowly. S.aureus. Enterococci are inhibited but not destroyed at therapeutically viable concentrations. Some strains of Staphylococcus aureus may be sensitive to methicillin, while others are resistant. The minimum inhibitory concentrations (MICs) of vancomycin range from 0.25 to 4.0 mg/L, making it compatible with the majority of Staphylococcus aureus and coagulase-negative staphylococci. It wasn't until 1987 that a Staphylococcus strain that was resistant to coagulase was first documented. A lot of S. aureus and S. strains. Also, epidermidis are less susceptible to vancomycin, according to the research. The first S. is further explained in this chapter. A wounded Japanese infant in 1996 developed an infection while using vancomycin to treat methicillin-resistant Staphylococcus aureus. A Staphylococcus aureus isolate was identified in the sample that had a minimum inhibitory concentration (MIC) for the antibiotic greater than 4 mg/L. Further, there are S. Staphylococcus aureus is resistant to vancomycin's bactericidal effects because it does not have autolysins.[15]

Vancomycin is effective against a wide variety of streptococci, including those with viridian, anaerobic, or microaerophilic characteristics, and against penicillin-sensitive or -resistant pneumococci. Although there have been known treatment failures, most Listeria monocytogenes isolates may be inhibited by vancomycin at clinically viable doses. There is no evidence that C. and other coliform bacteria produce diphtheroid hormones. In a well-regulated laboratory environment, it is applied to the jeikeium. Opportunistic infections that are resistant to vancomycin include Lactobacillus, Leuconostoc, and Pediococcus, among others. Two kinds of clostridium, anaerobic and microaerophilic streptococcus, and other bacteria are all successfully killed by vancomycin. Organisms, including C. challenging. Some actinomycetes are sensitive, whereas others are resistant, such as Bacteroides species and other anaerobes that do not produce oxygen. When it comes to mycobacteria, chlamydia, rickettsiae, and Enterobacteriaceae, vancomycin is completely ineffective.[16]

- *Teicoplanin*

Vancomycin is more effective than teicoplanin in killing Gram-positive bacteria. Dormant cells are not susceptible to teicoplanin's ability to kill microbes. The average minimum inhibitory concentration (MIC90) for methicillin-resistant and susceptible Staphylococcus aureus (MRSA) is between 0.2 and 1.5 mg/L, but the sensitivity of coagulase-negative staphylococci is more variable, ranging from 2 to 4 mg/L. It appears that the mechanism of action is comparable to that of vancomycin. According to Aldridge, a teicoplanin MIC90 of 16 mg/L or higher was observed for Staphylococcus epidermidis. Septic shock is another term for septic shock. Species homo sapiens, S. Alfredo Walter, and Ricardo S. Xylosis may occur. Tecoplanin kills all strains of Staphylococcus saprophyticus. The percentage of oxacillin-resistant coagulase-negative Staphylococci in the United Kingdom and Ireland is 23.4% (MIC = 8 mg/L [I]) and 7.6% (MIC > 8 mg/L [R]), respectively, according to blood culture results. This is in contrast to the percentage of oxacillin-susceptible Staphylococci in these countries, which is 7.6%. In vitro, teicoplanin is more effective than vancomycin against most streptococcal species, including Streptococcus pneumoniae, with MIC50 values of 0.25-0.5 and MIC90 values of 0.5-1 mg/L, respectively. The minimum inhibitory concentration (MIC90) for vancomycin is 1.56–4.0 mg/L, while the MIC90 for enterococci is 0.2–3.1 mg/L. The bactericidal action of tecoplanin on Enterococcus faecalis is quite weak.[17] Tecoplanin inhibits the development of several Gram-positive bacteria, including those that grow aerobically and those that grow anaerobically. Germs such as Propionibacterium acnes, Clostridium (including C. difficile), Bacillus species, Listeria monocytogenes, and Corynebacteria are unable to develop in environments where teicoplanin levels are low. Between 900.3 and 0.8 mg/L was the mean MIC for these microorganisms. Species of Mycobacterium, fungus, or Gram-negative bacteria are not susceptible. Tecoplanin has a 50% efficacy against staphylococcal and enterococcal bacteria when used in conjunction with aminoglycosides. When it comes to post-antibiotic action, teicoplanin outperforms vancomycin at comparable dosages in the case of E. coli. Faecalis is a kind of bacteria. The therapeutic significance of species of Leuconostoc, Pediococcus, and Lactobacillus is compromised due to the inherent resistance of these species to teicoplanin. The first notice of Enterococcus species developing resistance to glycopeptides occurred in 1988. It is now well recognised that there are several resistance patterns to vancomycin and teicoplanin. These patterns include VanA, VanB, VanC, VanD, VanE, and VanG. Plasmids allow enterococci to transmit resistance to vancomycin and teicoplanin from one generation to the next. The E. coli vancomycin resistance can be induced or exists naturally in the bacteria. However, this particular E.[16, 17] coli strain demonstrates inducible resistance to teicoplanin and has a MIC of 2 mg/L or lower. The presence of teicoplanin and vancomycin-resistant faeces was confirmed by VanD. S. Hemolyticus without teicoplanin response after cardiac surgery (MIC 16 mg/L) was initially reported by In their investigation, they documented the growth of S. Serially separated Staphylococcus aureus isolates were not resistant to plasmids. Pathogens isolated from an individual receiving treatment for endocarditis. S. vancomycin, an intermediate drug. Staphylococcus aureus (VISA) infections have been associated with treatment failures when the minimum inhibitory concentration (MIC) was 8 mg/L. The thickening of the bacterial cell wall caused by the increased synthesis of PBP2 and PBP2' makes antibiotics unable to reach the target

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areas in VISA strains. Teicoplanin has a much higher minimum inhibitory concentration (MIC) than vancomycin does for a number of bacteria, ranging from 8 to 32 mg/L.[17, 18]

➢ *Oritavancin*

To prevent oritavancin from adhering to plastic surfaces in the presence of 0.002% polysorbate 80, the minimum inhibitory concentration (MIC) of the medicine has to be determined. Before the change in conventional methodology, the drug's effectiveness was grossly understated in all published statistics. Nevertheless, as per the most recent guidelines from the Clinical and Laboratory Standards Institute (CLSI), the inclusion of polysorbate 80 reduces minimum inhibitory concentrations (MICs) for staphylococci and enterococci by a factor of 4 to 64. Conversely, streptococci are completely unable to infect them. Oritavancin has remarkable efficacy against staphylococci, enterococci, and streptococci, regardless of resistance phenotype. The fact that it is effective against VISA and VRSA strains is remarkable, even though its MICs are somewhat higher than those of the majority of vancomycin-susceptible bacteria. Oritavancin is efficient against a wide variety of Gram-positive bacteria and viruses, including Bacillus species. This includes Listeria monocytogenes in vitro. In addition, compared to vancomycin and metronidazole, oritavancin has MICs that are 2-4 times lower against three significant anaerobic species: Clostridium perfringens, Clostridium difficile, and Propionibacterium acnes. Challenging. Lactobacillus species, Pediococcus species, and Enterococcus species. There was a minimum inhibitory concentration (MIC) of 8 mg/L or below for oritavancin, and the microbes in question were resistant to vancomycin.[19]

➢ *Telavancin*

Testing 2-4 dilutions of telavancin against S. aureus allowed for a comparison between vancomycin and telavancin. Microorganisms and S. epidermidis, regardless of whether they are susceptible to or resistant to methicillin. Lower (1 mg/L) MICs are seen for isolates of MRSA and VISA. The bacterium telavancin is highly effective against a wide variety of streptococci. The antibiotic has comparable efficacy to vancomycin against susceptible enterococci, but its minimum inhibitory concentrations (MICs) are much higher against antibiotic-resistant bacteria. Telavancin also has antibacterial properties against several species of Corynebacterium and anaerobic Gram-positive bacteria. The MIC90 value for most isolates is less than 1 mg/L.[19, 20]

➢ *Dalbavancin*

The current recommendation from the CLSI for oritavancin susceptibility testing is to include 0.002% polysorbate 80. Improved accuracy and consistency in MIC measurements are the results of this process, which prevents the drug from sticking to plastic surfaces. No matter how much the minimum inhibitory concentration (MIC) increases (3-5 dilutions), dalbavancin's bactericidal properties are preserved in the presence of serum. This effect is brought about by the drug's strong protein binding. S. aureus and other Staphylococci, particularly those without coagulase, which makes them less effective against teicoplanin. Walcomycin and teicoplanin are not as effective against Staphylococcus aureus as dalbavancin. Microorganisms and S. Microbe that causes pneumonia. The number of S strains tested against dalabavancin is rather small, considering the number of glycopeptide-intermediate strains. Concentrations of 1 mg/L that limit aureus growth.[21] While glycopeptide-resistant bacteria are unaffected by dalfopristin, enterococci susceptible to vancomycin are effectively treated. A mere four times lower than teicoplanin's MIC50 indicates a negligible decrease. Because of its teicoplanin structure, it is ineffective against vanA enterococci and, by extension, VRSA. Because their trough dalbavancin levels are higher than the current MIC of the microbes of interest, in vivo selection of these mutants may be harder. However, serial passage has been employed to uncover sub-MIC dalbavancin-selective staphylococci subpopulations. The minimum inhibitory concentrations (MICs) of dalbavancin for anaerobes, such as Clostridium species, are 10 mg/L or lower, whereas for Corynebacterium species, they are 1 mg/L or below. When its MIC90 is below 0.125 mg/L, and anaerobic gram-positive cocci.[22]

V. ADVERSE EFFECTS

The Gram-positive bacteria are commonly treated with vancomycin and teicoplanin, although there is a risk that they can cause major adverse effects. The mechanism by which teicoplanin reduces the occurrence of side effects is still unclear.[18]

➢ *Nephrotoxicity*

Of the adverse effects of vancomycin, nephrotoxicity is the most famous. Although it can occur as late as 14 days after therapy, vancomycin-induced nephrotoxicity typically manifests between 5 and 7 days following administration. Ten percent to twenty percent of individuals receiving low-dose treatment and thirty to forty percent receiving high-dose therapy have experienced this. The medication does decrease renal function; however, the early nephrotoxicity was due more to formulation impurities than the drug itself. One possible explanation for renal tubular ischaemia is an upregulation of oxidative stress and reactive oxygen species production in the cells lining the proximal renal tubule [13, 23]. Additional evidence points to an energy-dependent basolateral membrane transport channel as the mechanism by which vancomycin causes nephrotoxicity in tubular cells. Vancomycin has an effect on the mitochondrial and reabsorptive functions of the cells in the proximal tubule. There are several potential mechanisms by which vancomycin might induce nephrotoxicity. Elyasi et al. discovered that higher dosages of vancomycin (>4 g/day) were associated with a higher risk of nephrotoxicity; however, their findings were derived from observational studies. Furthermore, nephrotoxicity was more common in patients given higher doses of vancomycin. Potential risk factors for vancomycin exposure include peak concentrations, greater nadir levels (>15-20 mg/L, particularly >20 mg/L), and the area under the time-concentration curve. Renal insufficiency is more likely to occur with prolonged usage of vancomycin. Elyasi et al.

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report that after one week of therapy, the risk of vancomycin-associated nephrotoxicity increases from 6% to 21%, and after two weeks, it approaches 30%. Though not often utilised, continuous vancomycin infusion was associated with a reduced incidence of nephrotoxicity compared to intermittent dosing.[23]

- *Red Man Syndrome*

Red man syndrome (RMS) is a side effect of vancomycin that affects between 5-50% of hospitalised patients and as many as 90% % of healthy control persons. Among the several possible symptoms of RMS are hypotension, generalised erythema, acute pruritis, urticaria, and flushing. Experts believe this to be a pseudo-allergic response to medicine that lacks an underlying immunological basis. Vancomycin stands out due to its ability to trigger mast cell degranulation and histamine release. The efficacy of opioids is enhanced when they are administered together.[24]

- *Neutropenia*

An absolute neutrophil count below 1000 microlitres is the hallmark of vancomycin-induced neutropenia, which affects 2% to 12% of patients. Neutropenia cases persist despite advances in formulation purity, which may indicate that previous medication formulations had contaminants that caused a greater proportion of adverse effects and so went unrecognised. The cause of vancomycin-induced neutropenia is still unclear, and it is unclear if the effect is immune-mediated. Vancomycin-induced neutropenia patients' bone marrow aspirates have revealed a spectrum of histological findings.[25]

VI. CONCLUSION

It is essential to consider possible side effects, such as nephrotoxicity and red man syndrome, when using these medicines. Commonly used antibiotics for Gram-positive bacteria, such as teicoplanin and vancomycin, can have serious side effects. Red man syndrome, neutropenia, and vancomycin-induced nephrotoxicity are some of the most serious side effects linked to its usage; each has its distinct processes and risk factors.

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